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Healing agent for wounds of the body surface.

COMPLETE SPECIFICATION

We, CHAS. PFIZER & CO., INC., a corporation organized under the laws of the state of Delaware, United States of America, of 11 Bartlett Street, Brooklyn, State of New York, United States of America do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to new and useful pharmaceutical compositions for promoting healing of wounds of the body surface.

In accordance with the present invention there is provided a pharmaceutical composition, for healing wounds of the body surface, in dosage unit form as hereinafter defined, comprising glucosamine and/or one or more derivatives of glucosamine as hereinafter defined, and a pharmaceutically acceptable carrier therefor.

As used herein the term dosage unit signifies a physically discrete unit containing an individual quantity of the active material in association with a pharmaceutically acceptable carrier, the quantity of active compound being such that one or more units are required for a single therapeutical administration. It does not include mere solutions in water or other common solvents except when such are packaged in ingestible containers or have been prepared so as to be acceptable for parenteral injection. Each dosage unit preferably contains not less than about 10 grams of the active material.

The healing of wounds of the body surface whether caused by trauma or surgery oftentimes presents considerable difficulty, as described in numerous articles appearing in the medical literature. Many persons exhibit a slow rate of healing during which time considerable care must be taken to avoid the possibility of infection. Even with persons of normal healing rate, protection against infection must be provided, necessitating exacting care by medical personnel. The present invention provides a new and effective process of facilitating the healing of wounds of the body surface which materially reduces the time during which the possibility of infection is greatest as well as the time periods of close medical care and supervision. Other beneficial results of the present process are obvious from the following disclosure. While beneficial results will be noted with even lesser amounts, it is usually desirable to administer the glucosamine compound at a dosage of at least from about 10 to about 20 grams per day for best results. Often times it is found advantageous to administer the glucosamine compound at dosages as high as 200 grams per day and even higher.

The physician will indicate daily dosage of the instant therapeutic agents. The dosage and the route of administration will depend upon the extent of the wound and the healing rate of the individual patient. The present therapeutic agents may be administered orally or locally, i.e. into the wound, and, at other times, parenterally, that is intravenously. Of course, these routes of administration may be employed concurrently to maintain an effective level of glucosamine compound in the subject patient. For example, the glucosamine compound may be administered to a patient orally at a dosage of from 10 to 20 grams per day for a period of four to five days before surgery, followed by intravenous administration at a dosage of between 100 to 200 grams in parenteral fluids, usually isotonic saline, for four to five days postoperatively and then oral administration, as needed, of from 10 to 20 grams per day, usually for an additional four to five days.

The pharmaceutical compositions of the present invention contain glucosamine, and/or glucosamine derivatives, which are lower N-alkanoylglucosamines, e.g. N-acetylgluco-

samine, phosphorylatedglucosamines, such as N-acetylglucosamine-6-phosphate, and glucosamine-6-phosphate, and salts of glucosamine with pharmaceutically-acceptable acids, such as hydrochloric, phosphoric, citric, gluconic, acetic, or malic acid. A particularly effective, and, for this reason, preferred, glucosamine derivative is N-acetylglucosamine. The therapeutic agent is conveniently administered in the form of a suspension, although it may also be administered as tablets or capsules. For oral use, suspensions of the therapeutic agent in pharmaceutically acceptable liquid media are particularly effective. Such liquid media are well known in the art, for example, aqueous glycols or sugar solutions, which may contain conventional flavoring and coloring agents. Tablets and capsules may be prepared from mixtures of the present compounds with well known pharmaceutical excipients such as starch, sugar, tapioca or certain forms of clay, such as kaolin, bentonite and Fuller's earth. For intravenous use, the present compounds are administered in isotonic solutions, such as isotonic saline.

For intravenous use, the present invention provides sterile aqueous compositions for intravenous administration which are prepared by dissolving the selected agent in an isotonic (about 0.1%) saline solution. It is preferred to employ the glucosamine compound at a concentration ranging from about 2% to about 20%, and preferably from 3% to 10%. Of course, lower concentrations provide some beneficial results but necessitate the use of extremely large volumes of intravenous solution which is usually not desirable. Higher concentrations, although operable, provide no appreciable advantage and thus are not recommended. The present invention also provides sterile solid compositions of glucosamine and/or glucosamine derivative as herein defined together with salt for reconstitution with water to provide the above-described intravenous compositions. Of course, such solid compositions should contain a sufficient amount of salt to provide an isotonic saline solution when dissolved in a certain amount of water, that is, an isotonic amount of salt. The solid compositions preferably contain salt and glucosamine compound in a weight ratio ranging from about 1:20 to about 1:200. For example, when one gram of sodium chloride and 50 grams of N-acetylglucosamine are dissolved in one liter of water, a 5% glucosamine isotonic saline solution is obtained. Other such isotonic solutions of the glucosamine compounds are prepared by reconstitution of the present solid compositions.

As a result of the administration of a glucosamine compound as herein described, in addition to a remarkable improvement in healing time, patients generally show a sense of well being, maintain body weight and, in some instances, unexpected weight gains are obtained. Further, such patients exhibit positive nitrogen balance in place of the usually expected negative balance during immediate postoperative period. Additionally, there is noted a lowering of blood cholesterol.

The following exemplifies the efficacy of the compositions of the invention in promoting wound-healing. A female patient of 19 years of age and average weight with a mid-thigh amputation suffered serious postoperative complication and poor wound healing. Daily intravenous administration of N-acetylglucosamine in isotonic saline (100 g. dissolved in 3 liters per day) to this patient for 4 days followed by daily oral administration of 20 grams of N-acetylglucosamine for 5 days resulted in a marked improvement in general condition with rapid healing of the wound.

A male patient of 28 years of age and average weight with postoperative septicemia and shock due to *E. Coli* was being treated hypothermia and with an artificial kidney for about three weeks. During this time his abdominal wound, i.e. the original operative incision, remained opened and gaping. At this time, the patient was treated with N-acetylglucosamine intravenously for 4 days, daily dosage being 100 grams in 3 liters of isotonic saline, followed by oral administration of 20 grams of N-acetylglucosamine daily for 5 days, which resulted in excellent, rapid healing of the wound. Similar results are obtained with glucosamine and other glucosamine derivatives as herein defined with human as well as animal subjects.

Similar results were obtained when the present process was used in the treatment of other surgical patients. The results are summarized in the following table:

NAG = N-Acetylglucosamine

PATIENT	DIAGNOSIS & OPERATION	PRE-OPERATIVE TREATMENT	POST-OPERATIVE TREATMENT	SERUM TRANS-AMINASE UNITS	BLOOD CHOLESTEROL mgm/100cc.	URINE N_2 gm.
			1st. P.O. day	Pre-op. 21	181	2.4
I	Ulcerative Colitis	NAG 10 gm.	NAG 100 gms. I.V.	1st. P.O. 46	163	
49 WF	Rx for several weeks with	daily for 4	2nd. P.O. day	4th. P.O. 23	144	.500
	300 mgm. cortisone daily	days	NAG 200 gms. I.V.	10th. P.O. 11	145	.145
	No complications		3rd. P.O. day			
	Discharged 11th P.O. day		NAG 250 gms. I.V.			
			4th. P.O. day			
			NAG 200 gms. I.V.			
II						
63 CF	Perforated Peptic	none	NAG 200 gm.	Pre-op 28	185	.500
	Ulcer, 3 days duration		I.V. daily for	1st. P.O. 47	160	.720
	No complications		5 days	4th. P.O. 26	173	.300
	Discharged 12th P.O. day			10th. P.O. 12	170	.100
III						
63 CM	Subtotal gastrectomy	NAG 10 gm.	NAG 200 gm. I.V.	Pre-op 19	204	.100
	chronic duodenal ulcer	daily for 4	daily for 3 days	1st. P.O. 41	210	.100
	Discharged 8th P.O. day	days		4th. P.O. 19	180	Balance
	No complications			8th. P.O. 4	170	Balance
IV						
39 CF	Acute + chronic	none	NAG 200 gm. I.V.	Pre-op 24	142	.400
	Cholecystitis		daily for 3 days	1st. P.O. 31	160	.400
	Cholecystectomy			4th. P.O. 20	160	.100
	No complications			10th. P.O. 8	130	Balance
	Discharged 10th P.O. day					

As it is obvious to those skilled in the art other therapeutically effective agents may be co-administered with the present agents, for example, compounds which serve as a source of high-energy phosporus. These compounds are described by A. H. Bryan and C. B. Bryan in "Bacteriology—Principles and Practices", Revised Fifth Edition, Barnes and Noble, Inc., New York, (1957), pages 382 to 385. Exemplary of this type of compound are phosphoenolpyruvic acid and adenosine phosphates, e.g. mono and di-phosphates, which aid in the phosphorylation of intermediates in the metabolism of carbohydrate. Other therapeutic agents which may similarly be employed are broad spectrum antibiotics such as tetracycline and oxytetracyline; ascorbic acid and tyrosine.

The following examples are given by way of illustration.

EXAMPLE I

A mixture of 100 g. of N-acetylglucosamine and 1 g. of sodium chloride is thoroughly blended in a twin shell blender in an ethylene oxide-carbon dioxide atmosphere. The mixture is stored in an infusion bottle for reconstitution with one liter of sterile water for intravenous administration.

Other such mixtures are prepared in the same manner to provide solid compositions containing the following weight proportions of salt to glucose amine compound:

1 part salt to 50 parts glucosamine.

1 part salt to 100 parts glucosamine hydrochloride.

1 part salt to 200 parts glucosamine phosphate.

1 part salt to 20 parts N-acetylglucosamine.

EXAMPLE II

Two thousand grams of N-acetylglucosamine is added to 20 liters of 0.1% aqueous saline solution. The resulting solution is filtered through a Seitz filter and stored in infusion bottles each containing one liter of 10% solution. The solution is useful for intravenous administration to human hosts with a wound of the body surface.

EXAMPLE III

The procedure of Example II is repeated to prepare the following solutions:

20% glucosamine in 0.1% saline.

3% N-acetylglucosamine in 0.1% saline.

2% glucosamine hydrochloride in 0.1% saline.

20% N-acetylglucosamine in 0.1% saline.

5% glucosamine phosphate in 0.1% saline.

5% glucosamine citrate in 0.1% saline.

10% glucosamine gluconate in 0.1% saline.

3% glucosamine acetate in 0.1% saline.

We are aware of Specification No. 819,122 which claims, *inter alia*, a therapeutic composition comprising a salt of glucosamine and 4,6-dihydroxyisophthalic acid, or 5-chloro-or 5-bromo-4,6-dihydroxyisophthalic acid and an inert solid carrier, or a composition comprising a salt of glucosamine and 5-iodo-4,6-dihydroxyisophthalic acid and an inert solid or liquid carrier, and we make no claim herein to these compositions.

Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:

1. A pharmaceutical composition, for healing of wounds of the body surface, in dosage unit form as hereinbefore defined, comprising glucosamine and/or one or more derivatives of glucosamine as defined herein and a pharmaceutically acceptable carrier therefor.

2. A composition according to claim 1 wherein the derivative of glucosamine is N-acetylglucosamine.

3. A pharmaceutical composition according to claim 1 or 2 containing an additional therapeutically effective agent as described herein.

4. A composition according to claim 3 wherein the therapeutically effective agent is a source of high energy phosphorus.

5. A composition according to any of the preceding claims wherein the pharmaceutically acceptable carrier is an isotonic solution or mixture.

6. A composition according to any of the preceding claims in which the concentration of the glucosamine compound is from about 2% to about 20% and preferably 3-10%.

7. A sterile solid composition comprising glucosamine, a salt thereof with a pharmaceutically acceptable acid, or N-acetylglucosamine, and an isotonic amount of sodium chloride.

8. A composition according to claim 7, in which the ratio of sodium chloride to the glucosamine compound is from about 1:20 to about 1:200.

9. The pharmaceutical compositions substantially as described herein with reference to the Examples.

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Reference has been directed, in pursuance of Section 8 of the Patents Act, 1949, to Specification No. 856493.

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